UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM:

To: Tim Ciarlo

From: Eric Bohnenblust, Ph.D., Entomologist

Secondary Review: Pesticide Efficacy Review Committee (PERC)

Date: April 6, 2016

Subject: PRODUCT PERFORMANCE DATA EVALUATION RECORD (DER)

THIS DER DOES NOT CONTAIN CONFIDENTIAL BUSINESS INFORMATION

Note: MRIDs found to be **unacceptable** to support label claims should be removed from the data matrix.

DP barcode: 432452
Decision no.: 507781
Submission no: 982694
Action code: R314
Product Name: SPCP4 Plus 1
EPA Reg. No or File Symbol: 2517-RTT
Formulation Type: Dog Collar
Ingredients statement from the label with PC codes included:
Deltamethrin 4.0% PC: 097805
Pyriproxyfen 1.0% PC: 129032
Application rate(s) of product and each active ingredient (lbs. or gallons/1000 square feet or per acre as appropriate; and g/m^2 or mg/cm^2 or mg/kg body weight as appropriate): Small collar 0.65 oz. fits up to 15" neck size; Medium collar 0.85 oz. fits up to 20" neck size; large collar 0.97 oz. fits up to 23" neck size
Use Patterns: Dog collar to control fleas and ticks.

I. Action Requested: Respond to rebuttal of previous efficacy review (DP 430469) which rejected efficacy claims against fleas and ticks resulting in a data deficiency for the proposed product.

II. Background: A previous efficacy review (DP 430469) rejected all proposed efficacy claims against ticks and fleas on the proposed product. The previous review found the data to support efficacy of the product against deer ticks and brown dog ticks; however, for any claims against ticks data are required showing efficacy of the product against a third tick species, either lone star ticks or American dog ticks.

III. MRID Summary:

49859801. Deltamethrin Pyriproxyfen Collar Response Report for Product Performance Studies Supporting SPCP4 Plus.

Registrant General Comment 1: MRID 43722809 was reviewed in November of 1995 and found to be acceptable to support the claims. …However, for some unknown reason, the Agency decided to re-review this study. Although

previously reviewed studies may be re-reviewed as part of the Registration Review process, acceptable studies are not generally re-reviewed for new registrations. As such, the re-review of this study is a departure from the Agency's standard practice.

Agency Response to General Comment 1: The Agency can review data, both new and old, to determine if the proposed efficacy claims on products are supported by the submitted/cited data. There are many reasons why the Agency may re-review studies and many situations when re-review of studies is necessary outside of the Registration Review or reregistration process.

Registrant General Comment 2: Original vs. Generic Products
To date there are six dog collars containing 4% deltamethrin that are registered with the Agency (Table 2). All six of these dog collars are registered based on the same flea and tick efficacy studies that were cited in this pending application. Please refer to Appendix 2 for a copy of the original EPA DERs. The Agency cannot register six 4% deltamethrin dog collars and then deny the registration of a seventh collar when all of the registrations are based on the same efficacy data.

Response to Registrant General Comment 2: The product is not considered a me-too product; therefore, we reviewed the specific subset of deltamethrin collar studies you cited to support your product and determined that the data do not support the label claims proposed. Because you are supporting the product through a selective citation and not a cite-all, we can only consider the specific studies you listed in your data matrix.

Registrant Rebuttal Point 1: MRID 43722809 does not document the quantity of pyriproxyfen. The original DER states that the percentage of pyriproxyfen in the product for which the MRID was initially submitted to support.

Agency Response to Rebuttal Point 1: The previous review documents the percentage of active ingredient of a proposed but unregistered product. However, while the title for the MRID contains the product name, the test substance is referred to as 3M nylar collars and no percentage of active ingredient is provided in the MRID document. Therefore, we cannot confirm that the product tested in the MRID was the unregistered collar that the study was submitted to support.

Registrant Rebuttal Point 2: "Methods for adult efficacy were not adequately provided." The goals of the study were two-fold to investigate the adulticidal and ovidical effects of pyriproxyfen against fleas. Seargent's is only citing the IGR effects of pyriproxyfen in preventing immature fleas from reaching the adult stage. Therefore, for this regulatory action, the results of the adulticidal portion of the study are irrelevant. It is worth noting that the ovicidal portion of the study is somewhat of a misnomer since it not only assessed egg eclosion, but also documented the percentage of fleas that successfully developed to the adult stage.

While the documentation of egg hatch provides interesting data, the relevant data are those documenting the number of fleas that reach the adult stage. As described in the report, and based on the equation used to assess product performance (equation 1) the number of fleas that reach the adult stage is less than $\leq 10\%$ of the number of fleas that developed into adults in the untreated control, group. Therefore reason # 2 which questions the adulticidal portion of this study should not be considered when reviewing this report.

Agency Response to Rebuttal Point 2: We note the registrant's request to only cite the IGR effects against fleas, however, the entire MRID will be reviewed to determine which specific claims it may support. The proposed label contains efficacy claims against adult fleas, so we documented the results and problems with the adulticidal portion of the study. Acknowledging that a study does not support adulticidal claims does not mean that a study cannot support IGR claims.

Registrant Rebuttal Point 3: Product performance is expressed as a ratio of the effects of a treatment as compared to the untreated control (Equation 1). The percent control is simply the measurement of adult fleas that developed from the eggs; this is the important parameter to measure when assessing the effectiveness of pyriproxyfen as an

IGR. Whether percent control was calculated using adults as a subset of eggs, larvae or pupae, has no bearing on the acceptability of the study. While the percent control varies depending on the subset used (Table 1), ultimately control is measured as the percentage of the F2 cohort that reaches the pest stage. In other words, the bottom line is the percentage of adults as a subset of the eggs in the cohort….The reviewer states that the study does not clearly identify the total number of fleas that emerged from the F2 cohorts. Specifically the reviewer was uncertain whether the adults and larvae were considered separately or together. This same issue is also described in the result section of the review: *"(3) Results: Both collar treatments reduced the emergence of fleas by over 90% through day 367. In the control treatment, 30-50% of the eggs hatched into larvae on most evaluation dates. Adult emergence was low for most of the study, but it is unclear if the number of adults recorded was a subset of larval emergence or in addition to larval emergence."*

As described above, pyriproxyfen is acting on flea development to prevent the flea from reaching the adult stage. Therefore the critical measure is the number of fleas that successfully develop to the adult stage. While documenting the portions of eggs that eclose, the number of larvae that pupate and the number of pupae that develop to adults, is informative, the only important measurement is the number of fleas that reach the adult stage. Whether this percentage is expressed as the percent pupae that develop to adults, the number of larvae that develop to adults or the number of eggs that develop to adults, is inconsequential since the number of the F2 generation (eggs) that reached adulthood will always be the smallest value and therefore demonstrate the highest level of control (Table 1). As indicated (Table 1) if the percentage of adults turns out to be a subset of the larvae counted, then the percentage of adults as a subset of the number of eggs collected would be even smaller. Based on the equation used to calculate product performance (Equation 1), the smaller the percentage, the greater the control. Knowing whether the percentage of adults represents the subset of pupae, larvae or eggs is not critical as long as the value is <10% of the same value in the untreated control group.

Agency Response to Rebuttal Point 3: Because there are ovicidal claims on the proposed label, egg hatch is an important endpoint because ovicidal claims are supported by data showing egg mortality. Regarding the percentage of hatched larvae and adults, in some instances, the number of developed adults is higher than the total larval count. The study states that 30-50% of eggs hatched into larvae in the control treatment. If we account for only the number of larvae that were counted, then typically only 30-50% of the eggs hatched. However, if these larvae then emerge into adults the number of live developed adults could never be higher than the number of larvae. If the number of live adults developed is independent of the number of larvae then egg hatch in many cases could be considerably higher than reported and that would provide more confidence in the study. However, if the number of live adults is a subset of the number of larvae, then in some instances egg hatch would be closer to 10% of the total ova collected in the control treatment which would reduce confidence in the study (see table 22 below for an example). Further, if adult emergence in the control is a subset of larval emergence, then the percentage of adults emerging in the control is considerably lower than the percentage of eggs hatching, which brings into question the viability of the fleas tested in the control treatment. Therefore, without a clear explanation we cannot assume the best case scenario for egg hatch, and adequate and consistent emergence of flea larvae and adults in the control treatment are critical for assessing the effect of the active ingredient in question. The argument presented in the rebuttal point 3 regarding the equation used to calculate efficacy is acceptable, the issue with the study is more a question of viability of the fleas in the control treatment.

TABLE 22

PERCENT OF LIVE ADULT FLEAS DEVELOPED FROM TEST DAY 206
OVA COLLECTION AND OVICIDAL EFFICACY

P.M. COLLECTION

TEST GROUP	TOTAL OVA COLLECTED	TOTAL LARVAL CT.	PERCENT LIVE DEVELOPED	PERCENT OVICIDAL EFFICACY
A	465	6	0	100
B	460	0	0	100
C	435	58	33	-

A= 3M NYLAR COLLAR (Lot No. 93709113 A2,A3,A4,A6,A7,A8)
B= 3M NYLAR COLLAR (Lot No. 93709113 B1,B2,B3,B5,B7,B10)
C= UNTREATED CONTROLS

Registrant Rebuttal Point 4: The reviewer states that it is not possible to know what the percentage of live adults is referencing. The percentage of live adults is a measure of the fleas within each cohort that reach the adult stage. Based upon information from the universities of California and Florida, at typical room temperatures, the flea will develop from egg to adult within 18 days (Zentko and Richman 1997; Rust 2010). Based on the study design, adults were counted 21, 28 and 35 days after collecting the eggs. These observation intervals allow the researcher to count the live adults over a three week interval. Counting live fleas on a weekly basis is a sound design because the survival of adult fleas remaining off the host is ca. 7.8 days (Hinkle, Koehler et al. 1998). Remembering that the flea eggs were placed in petri dishes along with larvae media, it is not unreasonable to assume that counting live adults may have been the simplest way for researchers to keep track of fleas reaching the adult stage. It would be difficult to assess adult emergence by sifting through the contents of the larval media because opening the petri dishes would result in the loss of adults due to their escape response.

Agency Response to Rebuttal Point 4: The tables presented in the MRID have a column for percent live developed and percent ovicidal efficacy. In the column for the percent live developed, the number presented in the control treatment appear to be the number of adults developed and not the percent of adults developed. However, in some instances the number in the percent adults developed is less than 100 which could be a percent or a number. This number makes a difference in how we assess emergence in the control treatment and we cannot know the intentions of the person who wrote the study over 20 years ago.

Registrant Rebuttal Point 5: The reviewer in not certain when the on animal portion of the study ended. The duration of the On-Animal portion of the study was for seven weeks. As explained above (Reason #2), the study consisted of two portions. While the goal of this study was two-fold, 1) to investigate the adulticidal and 2) the ovicidal effects of the pyriproxyfen against fleas. Sergeant's is only citing the IGR effects of pyriproxyfen in prohibiting immature fleas from reaching the adult stage. Therefore, for this regulatory action, the results of the adulticidal portion of the study are irrelevant. Part-One of the Study consisted of the adulticidal and the ovicidal portion and Part-Two of Study - Ovicidal Portion. The adulticidal portion of the study conducted on the animal was initiated on day 0 and ended on day 49 and Part-Two continued on the following infestation interval (day 63) through to the end of the year.

Agency Response to Rebuttal Point 5: We thank you for this clarification, this concern is clear.

Registrant Rebuttal Point 6: Rates of Development: The reviewer questions the development rate of the fleas. While temperature and other factors may affect flea development, the experimental design of this study is based on sound science. According to the entomologists from UC Riverside, and UF Gainesville (Zentko and Richman 1997; Rust 2010), flea eggs typically hatch within 2 days of oviposition; larvae typically reach pupation within 8-15 days and the flea typically reaches the adult stage within 18 days.

However, as described earlier in this rebuttal, the timing of egg eclosion is not the critical measurement. While it is interesting to document the number of larvae emerging from eggs, the only salient data are those values documenting the number of fleas of the F2 generation that reach the adult pest stage. As such, recording the exact number and timing of larvae that emerge from the eggs is less important than the number of adults counted on weeks 3, 4 and 5.

Agency Response to Rebuttal Point 6: While the timing of egg eclosion is not the critical measurement, the study director acknowledges in the report that larval emergence is erratic and in a number of instances low. The study director displayed enough concern about possible contamination to test dog hair from the control animals for pyriproxyfen. While the results of that testing were inconclusive, this along with the concern about how adult emergence is reported and characterized raises significant questions about the viability of the data collected from the control animals.

Conclusion: UNACCEPTABLE. This rebuttal MRID does not support any additional pests that were not already supported in the previous DP (430469).

IV. EXECUTIVE DATA SUMMARY:

(A) The rebuttal does not support any additional pests that were not already supported in the previous review (DP 430469).

V. LABEL RECOMMENDATIONS:

(1) There are no new changes needed to the directions for use.

(2) The following marketing claims are acceptable: No marketing claims are acceptable.

(3) The following marketing claims are unacceptable: N/A

(4) The following MRIDs should be removed from the data matrix, as they are classified as “unacceptable” to support the product: 49859801